

Application No. 10/792,307

Reply to Office Action

*REMARKS/ARGUMENTS**The Pending Claims*

Claims 1, 3, 5-12, 20-23, and 32-45 currently are pending. Claims 9, 10, and 20-23 are withdrawn from consideration as being drawn to a non-elected invention. New claims 32-45 have been added, of which claims 34-45 correspond to non-elected subject matter. Accordingly, claims 34-45 also are withdrawn.

The Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the present invention.

Claims 1 and 5 have been amended to recite an isolated or purified nucleic acid molecule that comprises SEQ ID NO: 3 (claim 1) or comprises a nucleotide sequence complementary to SEQ ID NO: 3 (claim 5). Claims 3 and 6 have been amended to recite an isolated or purified nucleic acid molecule comprising a nucleotide sequence encoding the amino acid sequence of SEQ ID NO: 4 (claim 3) or a nucleotide sequence complementary thereto (claim 6). Claims 3 and 6 also have been re-written in independent claim form. These amendments are supported by the original claims, and by the specification at, for example, paragraph [0023].

Withdrawn claims 9 and 10 have been amended to delete the phrase "optionally in the form of a vector," which subject matter is recited in newly added dependent claims. Withdrawn claims 20-23 have been amended to recite that a wild-type TDC2 gene encodes SEQ ID NO: 4. This amendment is supported by the specification at, for example, paragraph [0023].

Claims 32-45 are new and are supported by original claims 7-12, and by the specification at, for example, paragraphs [0041], [0046], and [0061]. Claims 2, 4, 13-19, and 24-31 have been cancelled, without prejudice, as being drawn to a non-elected invention.

No new matter has been added by way of these amendments.

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The Office Action

The Office Action requires affirmation of the telephonic claim and species election made on November 9, 2005. The claim and species election is discussed below.

The Office Action rejects claims 3 and 6 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office Action also rejects claims 1-3, 5-8, and 11-12 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

The Office Action rejects claims 1-3, 5-7, 8, 11, and 12 under 35 U.S.C. § 102(b) or 35 U.S.C. § 103(a) as allegedly anticipated by, or obvious in view of, the following references: Kurima et al., *Nature Genetics*, 30: 277-284 (2002) ("the Kurima reference"), WO 01/75067 (Drmanac et al.) ("the Drmanac PCT application"), and WO 02/068579 (Venter et al.) ("the Venter PCT application").

In addition, the Office Action provisionally rejects claims 1-3, 5-8, 11, and 12 under 35 U.S.C. § 101 as allegedly claiming the same subject matter recited in claims 7-9, 11, 12, 15, 16, 23, and 24 of copending Application No. 10/487,887.

Reconsideration of the rejections is respectfully requested for the reasons discussed below.

The Information Disclosure Statement

The Office Action states that the Information Disclosure Statement (IDS) filed on March 3, 2004 has been considered with the exception of reference AJ, which was not submitted with the IDS as filed. Applicants submit herewith a copy of reference AJ for consideration.

Confirmation of the Election

Applicants confirm the election, with traverse, of the claims of Group I (i.e., claims 1-8, 11, and 12) and the species of SEQ ID NO: 3 and SEQ ID NO: 4. Claims 9, 10, 20-23, and 34-45 are withdrawn from further consideration as being drawn to a non-elected invention.

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Discussion of the Section 112, Second Paragraph, Rejection

The Office Action rejects claims 3 and 6 as allegedly indefinite under Section 112, second paragraph, for recitation of the term "moderately stringent conditions." The pending claims, as amended, do not contain the allegedly objectionable term. Accordingly, the Section 112, second paragraph, rejection is moot in view of the amended claims and should be withdrawn.

Discussion of the Section 112, First Paragraph, Rejection

The Office Action rejects claims 1-3, 5-8, and 11-12 under Section 112, first paragraph, as allegedly lacking enablement for fragments of specifically recited sequences or molecules that hybridize or share at least 49% identity to such sequences. The Office Action acknowledges, however, that an isolated or purified nucleic acid comprising SEQ ID NO: 3, or comprising a nucleotide sequence encoding SEQ ID NO: 4, is enabled.

Solely in an effort to advance prosecution of the subject application, and not in acquiescence of the rejection, claims 1 and 3 have been amended to recite an isolated or purified nucleic acid molecule comprising SEQ ID NO: 3 or comprising a nucleotide sequence encoding SEQ ID NO: 4. Similarly, claims 5 and 6 has been amended to recite an isolated or purified nucleic acid molecule comprising a nucleotide sequence that is complementary to an isolated or purified nucleic acid molecule comprising SEQ ID NO: 3 or comprising a nucleotide sequence that encodes SEQ ID NO: 4. All other claims depend from claims 1, 3, 5, or 6. Accordingly, Applicants request withdrawal of the Section 112, first paragraph, rejection as moot in view of the amended claims.

Discussion of Prior Art Rejections

Claims 1-3, 5, 6, 8, 11, and 12 are rejected as allegedly anticipated by, or obvious in view of, the Kurima reference, the Drmanac PCT application, and the Venter PCT application, either alone or in combination. Specifically, the Office Action contends that the Kurima reference discloses a DNA sequence encoding TDC2 that is 100% identical to SEQ ID NO: 3, and the Drmanac PCT application and Venter PCT application each allegedly discloses a nucleic acid sequence that (i) is a fragment of SEQ ID NO: 3, (ii) hybridizes to the

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complement of SEQ ID NO: 3 under moderately stringent conditions, or (iii) shares 49% or more identity with SEQ ID NO: 3.

Contrary to the Office Action, the Kurima reference does not disclose an isolated or purified nucleic acid molecule comprising SEQ ID NO: 3. Alignment of the Kimura sequence with SEQ ID NO: 3 of the present application, shows that the Kimura sequence contains only nucleotides 48-3121 of SEQ ID NO: 3; it does not contain residues 1-47 of SEQ ID NO:3 (copy of sequence alignment enclosed). Thus, the Kurima reference does not disclose or suggest an isolated or purified nucleic acid molecule comprising SEQ ID NO: 3, or a sequence complementary thereto. Similarly, the Kimura reference does not disclose or suggest a nucleic acid sequence that encodes SEQ ID NO: 4. Accordingly, the Kimura reference does not disclose or suggest the subject matter of the pending claims.

The Drmanac and Venter PCT applications similarly fail to disclose or suggest a nucleic acid molecule that comprises SEQ ID NO: 3 or encodes SEQ ID NO: 4. Thus, the Drmanac and Venter PCT applications do not disclose or suggest the subject matter of the pending claims, whether considered alone or in combination with the Kimura reference.

As the cited references do not disclose or suggest the subject matter of the pending claims, such references cannot properly be considered to anticipate or render obvious the claimed subject matter. Accordingly, the rejections under Sections 102(b) and 103(a) should be withdrawn.

Discussion of Double Patenting Rejection

Claims 1-3, 5-8, 11, and 12 are provisionally rejected under section 101 as allegedly claiming the same subject matter as that recited in claims 7-9, 11, 12, 15, 16, 23, and 24 of copending Application No. 10/487,887. The '887 application was subject to a telephonic restriction requirement, in response to which claims 7-9, 11, 12, 15, 16, 23, and 24 were not elected for further prosecution. As such, claims 7-9, 11, 12, 15, 16, 23, and 24 of the '887 application are withdrawn from consideration. Accordingly, the Section 101 double patenting rejection is moot and should be withdrawn.

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Request for Rejoinder

Applicants' request reconsideration of the restriction requirement and rejoinder of the non-elected claims.

A restriction of claims is proper only when the Office can show an undue burden would be placed on the Examiner if the restricted claims were examined together. In this case, all of the non-elected claims depend from, or otherwise include, all of the elements of the elected claims, and there would be no undue burden would be placed on the Examiner if all claims were examined together. In particular, the elected claims are directed to isolated or purified nucleic acids, vectors comprising the nucleic acids, and cells comprising the vectors or nucleic acids. The non-elected claims recite, for example, a pharmaceutical composition comprising the same nucleic acids or vectors, along with a carrier (e.g., claims 9, 10, and 34-45). The Office has not shown that the inclusion in the dependent claims of a "carrier" results in any undue burden in searching or examining these composition claims in addition to the elected claims. Accordingly, the restriction requirement should be withdrawn, at the very least, with respect to the pharmaceutical composition claims.

Even if the restriction requirement is deemed proper, the rejoinder rules provide that, when claims to a product are elected for examination in response to a restriction requirement and are subsequently found to be in condition for allowance, any non-elected product or process claims that depend from, or otherwise include, all of the elements of the allowable product claims should be rejoined. M.P.E.P. § 821.04.

As previously mentioned, each of the non-elected claims (e.g., claims 9, 10, 20-23, and 32-45) depend from, or otherwise include, all of the elements of claims 1, 3, 5, or 6. Accordingly, upon a finding that the elected claims are in condition for allowance, the non-elected claims should be rejoined for examination.


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Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: March 14, 2006

Amendment or ROA - Regular (Revised 2005 11 04)

[948] Candidate gene analysis of DFNA25, a novel locus responsible for autosomal dominant, high frequency, nonsyndromic hearing loss

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DFNA25 is a novel locus responsible for autosomal dominant, delayed onset, progressive, high frequency, nonsyndromic hearing loss in a large family of Bohemian descent. Haplotype analysis revealed recombination events between D12S327 and D12S1051 in 4 affected individuals and a recombination event between D12S1030 and D12S84 in one affected individual. The DFNA25 interval is thus defined by D12S327 (centromeric) and D12S84 (telomeric), a 20 cM region of chromosome 12q21-24. The maximum two-point LOD score was 6.82 at $\theta = 0.041$ for D12S1030.

Candidate genes lying within the DFNA25 interval include UBE3B, ATP2A2, ATP2B1, zfOCL, LTA4H, and PAH. BAC contigs lying within the DFNA25 genetic interval were identified (Baylor HGSC). Polymorphic markers mapping to BACs containing candidate genes of interest were genotyped in the family members to assess for recombination events that would allow exclusion of the BAC from the candidate region. The marker RK341/301 colocalizes to the same BAC in 12q24 as the UBE3B gene and was informative in the DFNA25 family. UBE3B is a member of the E3 ubiquitin ligase family involved in cellular homeostasis and apoptosis (Ciechanover et al. 1991) and upregulation of its mRNA has been observed after noise exposure in the chick (Lomax et al. 2000).

ATP2A2 is a calcium channel gene related to *Atp2b2*, which is known to be mutated in deafwaddler (*dww*) mice (Street et al. 1998). Mutations in ATP2A2 cause Darier-White disease, which is involved in intercellular communication between epidermal cells, similar to the role of connexin 26 (*GJB2*) and connexin 31 (*GJB3*). D12S2398 was confirmed by BLAST to map to the same BAC as ATP2A2, and this marker was genotyped in the DFNA25 family.

For BACs lacking described polymorphic markers, novel polymorphic markers were developed by screening the sequence for short tandem repeats (STRs), designing PCR primers, amplifying the STR sequence in genomic DNA of unrelated controls, and assessing the heterozygosity of the marker using SSCP.

[949] Genetic map localization of DFNA34 and DFNA36, two novel autosomal dominant nonsyndromic deafness loci

**Kiyoto Kurima*, National Institutes of Health, National Institute on Deafness and Other Communication Disorders, Rockville, MD; Yvonne Szymko, Bethesda, Maryland; Susan F. Rudy, National Institutes of Health, National Institute on Deafness and Other Communication Disorders, Bethesda, MD; Robert J. Morrell, National Institutes of Health, National Institute on Deafness and Other Communication Disorders, Rockville, MD; Thomas B. Friedman, National Institutes of Health, National Institute on Deafness and Other Communication Disorders, Rockville, MD; Andrew J. Griffith, National Institutes of Health, National Institute on Deafness and Other Communication Disor, Rockville, Maryland.

Hereditary deafness is genetically heterogeneous, and it is estimated that hundreds of genes may cause nonsyndromic sensorineural deafness. The identification of these genes associated with hearing loss continues to reveal the molecular mechanisms underlying the evolution, development, structure, and physiology of the auditory system, as well as the pathogenesis of hereditary hearing loss.

We have ascertained two families, LMG113 and LMG128, segregating autosomal dominant, progressive, postlingual, nonsyndromic sensorineural hearing loss. LMG128 segregates a postlingual auditory phenotype whose onset occurs during the first decade of life and rapidly progresses to profound deafness by early adulthood, whereas LMG113 segregates a less

severe phenotype that becomes clinically detectable during the third or fourth decade of life and progresses at a much slower rate.

Genotype analysis excluded linkage to known deafness loci in both families. A genome-wide linkage scan with STR markers revealed linkage of the deafness phenotype in LMG113 to a 14-cM region between markers D1S102 and D1S3739 on chromosome 1q44 (maximum 2-point LOD = 3.33 at $\theta = 0$ for D1S2836). DFNA34 co-localizes with the locus for Muckle-Wells syndrome (MWS), a dominant disorder characterized by systemic inflammatory features and progressive sensorineural deafness. The auditory phenotypic overlap between DFNA34 and MWS raises the possibility that DFNA34 and MWS may be allelic.

Sensorineural hearing loss in LMG128 was linked to a 12 cM region between markers D9S1118 and D9S175 on chromosome 9q13-q21 (maximum LOD = 6.31 at $\theta = 0$ for D9S1124). The DFNA36 critical interval co-localizes with the DFNB7/11 locus, suggesting that these loci may represent allelic disorders.

Linkage analyses of additional families such as LMG113 and LMG128 will contribute toward the localization of novel loci, as well as the identification of deafness genes that have been localized but not previously cloned.

[950] Mutations in the transcriptional activator EYA4 cause late-onset deafness at the DFNA10 locus

**Sigrid Wayne*, University of Iowa, Iowa City, Iowa; Nahid G. Robertson, Brigham and Women's Hospital and Harvard Medical School, Pathology, Obstetrics, Gynecology, and Reproductive Biology, Boston, MA; Frank Declau, University of Antwerp, Medical Genetics, Antwerp; Nancy Chen, UCSD and VA Medical Center, Surgery/Otolaryngology and Neurosciences, La Jolla, CA; Kristien Verhoeven, University of Antwerp, Medical Genetics, Antwerp; Sai Prasad, University of Iowa, Otolaryngology-Head and Neck Surgery, Iowa City, IA; Cynthia C. Morton, Brigham and Women's Hospital, Boston, Massachusetts; Allen F. Ryan, University of California, San Diego, Neurosciences, La Jolla, California; Guy Van Camp, University of Antwerp, Medical Genetics, Antwerp; Richard J. Smith, University of Iowa, Otolaryngology, Iowa City, Iowa

Progressive late-onset sensorineural hearing loss, or presbycusis, is a major handicap for the elderly, and is thought to be caused by a complex interaction between environmental and genetic factors. The characterization of genes associated with presbycusis may foster the development of new habilitation options. DFNA10, a locus associated with autosomal dominant, progressive, late-onset sensorineural hearing loss is a potential gene involved in presbycusis. It was previously mapped to a 17 centimorgan (cM) interval on chromosome 6q22-23. In this work, we identified EYA4 (Eyes absent 4), a member of the vertebrate Eya family of transcriptional activators, as the causative gene of hearing loss at the DFNA10 locus.

EYA4 was an excellent candidate gene for DFNA10 in view of the association of syndromic hearing loss with mutations in another Eya gene, EYA1, in branchio-oto-renal syndrome. Two unrelated families from Belgium and America with DFNA10 hearing loss were screened for mutations in EYA4. We found different mutations in EYA4 segregating with the hearing loss in each family. Both mutations create premature stop codons, and are predicted to disrupt the conserved region of the protein. Cochlear Eya4 expression was examined by *in situ* hybridization, as well as by an analysis of alternative splicing in the cochlea. Eya4 is expressed in the neuroepithelium of the developing cochlea, and in cochlea-associated tissues post-natally. Developmentally regulated alternative splicing of Eya4 was detected in the cochlea.

Although EYA proteins interact with members of the PAX, SIX and DACH protein families in a conserved network that regulates early embryonic development, our findings show that EYA4 also is important post-developmentally for continued function of the mature organ of Corti.

Supported in part by NIH Otolaryngology Research Training Grant 5-T32-DC00040 (SW), and NIH grants DC03402 (CCM) and DC03544 (RJHS).

Blast Result

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Blast 2 Sequences results

PubMed

Entrez

BLAST

OMIM

Taxonomy

Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTN 2.2.13 [Nov-27-2005]

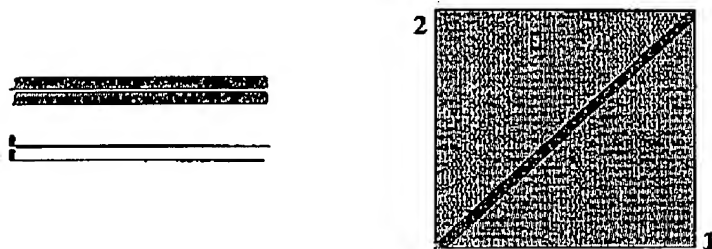
Match: 1 Mismatch: -2 gap open: 5 gap extension: 2
x_dropoff: 50 expect: 10.000 wordsize: 11 Filter ☒ View option: Standard
Masking character option: X for protein, n for nucleotide Masking color option: Black
☐ Show CDS translation ☐

Sequence 1: lcl|seq_1
Length = 3169 (1 .. 3169)

SEQ ID NO: 3

Sequence 2: gi|20304092|ref|NM_080751.1|Homo sapiens transmembrane channel-like 2 (TMC2), mRNA
Length = 3121 (1 .. 3121)

Kurima



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.

Score = 5884 bits (3060), Expect = 0.0
Identities = 3074/3074 (100%), Gaps = 0/3074 (0%)
Strand=Plus/Plus

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<http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi?0>

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<http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi?0>

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Query	1296	ATTTCTTCGTGTCCTGGCCAACTTTCTCATCATCTGCTGTTTGTGTGGAAGTGGGTACCT	1355
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<http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi?0>

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Query	2256	CCTGGGCAAGATCTTTGCTTTTCCTCGCCAATCCAGGCCTGATCATCCAGCCATCCTGCT	2315
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Query	2556	GGACAAGAAGGCGCAGGGCCCTGGGACCTCCAATTCTGCCAGCAGGACCACACTGCCTGC	2615
Sbjct	2508	GGACAAGAAGGCGCAGGGCCCTGGGACCTCCAATTCTGCCAGCAGGACCACACTGCCTGC	2567
Query	2616	CTCTGGACACCTTCCTATATCTCGGCCCCCTGGAATCGGACCAGATTCTGGCCACGCCCC	2675
Sbjct	2568	CTCTGGACACCTTCCTATATCTCGGCCCCCTGGAATCGGACCAGATTCTGGCCACGCCCC	2627
Query	2676	ATCTCAGACTCATCCGTGGAGGTCAGCCTCTGGAAAGAGTGCTCAGAGACCTCCCCACTG	2735
Sbjct	2628	ATCTCAGACTCATCCGTGGAGGTCAGCCTCTGGAAAGAGTGCTCAGAGACCTCCCCACTG	2687
Query	2736	ACGGCTAGGACTCCAGGGAGCCTCGACCCTAGGGCTGATCCTCAAGTACCCAGTTTCAC	2795
Sbjct	2688	ACGGCTAGGACTCCAGGGAGCCTCGACCCTAGGGCTGATCCTCAAGTACCCAGTTTCAC	2747
Query	2796	ACATACCAACCAAGGTTCTCTCCCTCTTTCTCTCTCACATACATGCTCTGTCTCCTCTC	2855
Sbjct	2748	ACATACCAACCAAGGTTCTCTCCCTCTTTCTCTCTCTCACATACATGCTCTGTCTCCTCTC	2807
Query	2856	TTGGAATGCATGAACCTTTGATTCTTCAGGCCCTTGTGAGCTACCGAAGGAGGAAGACAG	2915
Sbjct	2808	TTGGAATGCATGAACCTTTGATTCTTCAGGCCCTTGTGAGCTACCGAAGGAGGAAGACAG	2867
Query	2916	TGGCTTCACCTGTCTTTAGGGAAGCTGGAGCCATCTCTGCACTAACTGCCCTCCCAAAT	2975
Sbjct	2868	TGGCTTCACCTGTCTTTAGGGAAGCTGGAGCCATCTCTGCACTAACTGCCCTCCCAAAT	2927
Query	2976	ATCTTGGTTTCAGACAGCTCTGAACCCACGCTCAGAGTGGTTCGACCTTGCTCCCGATT	3035
Sbjct	2928	ATCTTGGTTTCAGACAGCTCTGAACCCACGCTCAGAGTGGTTCGACCTTGCTCCCGATT	2987
Query	3036	TCGGAGTTGGGGAAGGGCCATGACCACCCTCGTAGACTTTTCCATGGGATACAGTTTAG	3095
Sbjct	2988	TCGGAGTTGGGGAAGGGCCATGACCACCCTCGTAGACTTTTCCATGGGATACAGTTTAG	3047
Query	3096	GACACGGGTTTCTGCCAGCTTCCCTAACAGGAGGGGGATGGAGAAGGGCCTACATTTCT	3155
Sbjct	3048	GACACGGGTTTCTGCCAGCTTCCCTAACAGGAGGGGGATGGAGAAGGGCCTACATTTCT	3107
Query	3156	CAATCCAGAGGAAG	3169
Sbjct	3108	CAATCCAGAGGAAG	3121

<http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi?0>

Blast Result

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Score = 94.9 bits (49), Expect = 1e-15
Identities = 49/49 (100%), Gaps = 0/49 (0%)
Strand=Plus/Plus

Query 1 GCAGTGTCTGCTGACCATGAGCCACCAGGTAAAGGGCCTGAAAGAGGAAG 49
|||||
Sbjct 1 GCAGTGTCTGCTGACCATGAGCCACCAGGTAAAGGGCCTGAAAGAGGAAG 49

CPU time: 0.05 user secs. 0.01 sys. secs 0.06 total secs.

Lambda K H
1.33 0.621 1.12

Gapped
Lambda K H
1.33 0.621 1.12

Matrix: blastn matrix:1 -2
Gap Penalties: Existence: 5, Extension: 2
Number of Sequences: 1
Number of Hits to DB: 953
Number of extensions: 20
Number of successful extensions: 4
Number of sequences better than 10.0: 1
Number of HSP's gapped: 2
Number of HSP's successfully gapped: 2
Length of query: 3169
Length of database: 16,670,205,594
Length adjustment: 27
Effective length of query: 3142
Effective length of database: 16,670,205,567
Effective search space: 52377785891514
Effective search space used: 52377785891514
X1: 11 (21.1 bits)
X2: 26 (50.0 bits)
X3: 26 (50.0 bits)
S1: 14 (27.6 bits)
S2: 22 (43.0 bits)

<http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi?0>